IACM International Association of Color Manufacturers

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Dr. Scott Masten
NIEHS/NTP
P.O. Box 12233
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2 February 2001

RE: National Toxicology Program; Request for Comments on Substances Nominated to the National Toxicology Program (NTP) for Toxicological Studies. 65 Fed. Reg. 75727 (4 December 2000)

Dear Dr. Masten:

On behalf of the members of the International Association of Color Manufacturers (IACM), we submit these comments on the nomination of D&C Red No. 27/D&C Red No. 28 ("Red 27/28") for inclusion in the testing program administered by the National Toxicology Program (NTP). 65 Fed. Reg. 75727 (4 December 2000). IACM believes that the inclusion of Red 27/28 in the program is inconsistent with the criteria for the nomination and selection of substances for testing by NTP.

IACM is the international association of color additive manufacturers. IACM's members manufacture and market the vast majority of color additives (certified and exempt from certification) that are incorporated into foods, drugs and cosmetics in the United States. These color additives are extensively regulated by the U.S. Food and Drug Administration (FDA) as described at 21 C.F.R. Parts 73 and 74, and have been thoroughly evaluated to assure that they are safe for inclusion in foods, drugs, and cosmetics.

During the 1970s and 1980s, IACM's predecessor association, the Certified Color Manufacturers Association, participated in the design and conduct of a large number of lifetime toxicity/carcinogenicity studies of

certified color additives, including Red 27/28, pursuant to FDA's provisional listing regulations.* 21 CFR Part 81. These lifetime studies are described in the "background summary" for the nomination, "D&C Red No. 27/D&C Red No. 28" (dated October 2000), available on the NTP website.

The Nomination and Selection of Substances for Testing by NTP

The process by which substances are nominated and selected for testing by NTP is summarized in the current proposal, and in a previous proposal published in March 2000. 65 Fed. Reg. 11329 (2 March 2000). In this proposal, NTP stated,

> The NTP actively seeks to identify and select for study chemicals and agents with the highest potential for adversely impacting public health. . . . substances selected generally fall into two broad overlapping categories: (1) Those substances of greatest concern for public or occupational health based on the extent of human exposure and suspicion of toxicity, and (2) substances for which toxicological gaps exist and additional studies would aid in assessing potential human health risks by facilitating cross-species extrapolation and evaluation of dose-response relationships. 65 Fed. Reg. at 75727.

As can be readily seen, the available data on Red 27/28 do not indicate that it is a substance with great concern for public health, nor is it a substance for which significant "toxicological gaps" exist. Also, D&C Red 27/28 have an extremely low level of human exposure further alleviating concern about public health effects.

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*The majority of the provisionally listed color additives, including Red 27/28, were subsequently permanently listed at 21 CFR Part 74.

The Available Data Do Not Support the Need for Additional Testing

The color additives D&C Red No. 27/D&C Red No. 28 ("Red 27/28") are two color additives of very similar chemical structure (Red 28 is the disodium salt of Red 27) that have been approved for use in drugs and cosmetics for many years (21 CFR Secs. 74.1327, 74.1328, 74.2327, and 74.2328). The two color additives were found to be safe for their approved uses based on the same set of extensive safety studies.

Red 27/28 were nominated for testing in the NTP program by FDA. The background summary for the nomination provides a brief review of the safety studies and states,

> Our current knowledge of the photochemistry and the photobiology of D&C Red No. 27 and D&C Red No. 28 raises new concerns about the long-term safety of these colorants.

The extensive list of safety studies described in Section 6.1 of the nomination background summary do not suggest that Red 27/28 cause any significant toxic or carcinogenic effects. Even though these studies were not specifically designed to evaluate phototoxic or photocarcinogenic effects, the studies included extensive in-life and post mortem examinations and such effects would have been identified if they had been present.

It is important to note that among the extensive list of studies described in the nomination summary (Section 6.1) are a series of lifetime toxicity/carcinogenicity feeding studies in rats and mice that did not identify any compound related adverse effects of the consumption of Red 27. The animals were subjected to a normal daily cycle of light and dark throughout the studies.

During the course of these lifetime studies, the test animals received significant dermal exposure to the color additive on a daily basis through normal living conditions, and no adverse dermal effects were noted based on

regular in-life observations, and post-mortem gross pathology examinations, and histology. Furthermore, the nomination summary describes long-term dermal studies of Red 27 in rabbits and mice, conducted on abraded and intact skin, that did not reveal any compound related adverse effects. As with the lifetime studies, the animals were subjected to a normal daily cycle of light and dark.

The extensive available data demonstrate that Red 27/28 do not have significant potential to cause phototoxic or photocarcinogenic effects. If such potential existed, it would have been identified in the earlier studies.

Current Uses of Red 27/28 Do Not Result in Significant Exposure

The color additives D&C Red No. 27 and D&C Red No. 28 are approved by FDA for use in coloring drugs (21 CFR Secs. 74.1327 and 1328) and cosmetics (21 CFR Secs. 74.2327 and 2328). The color additives are subject to the FDA's certification requirements (21 CFR Part 80), and therefore accurate data are available on the amount certified and available for use. In 2000, 2,890 and 24,796 pounds of Red 27 and Red 28 dye, respectively, were certified by FDA for a total of 27,686 lbs. of both color additive dyes. The dye is used as such, and used to manufacture the lake (insoluble) form of the color additives.

Assuming that all of this color (27,686 lbs.) is consumed among the total U.S. population (276,059,000), a potential maximum human exposure from topical and ingested uses of 0.002 mg/kg/day can be determined. Consistent with the available toxicology data, this extremely low level of exposure is highly unlikely to result in any adverse health effects.

Development of Appropriate Testing Protocols

If NTP chooses to proceed with testing of Red 27/28, we request the opportunity to review and comment on the study protocols. Currently, the field of *in vitro* photogenotoxicity testing abounds with many studies in

which the experimental variables (conditions for photoactivation, effects of photoactivation on cell cytotoxicity, etc.) have not been adequately standardized.

It is incumbent on NTP to validate selected photogenotoxicity assays prior to investigating Red 27/28. As the NTP is well aware, the extrapolation of the results of validated *in vitro* assays in prokaryotic and isolated eukaryotic cell systems to the potential for genotoxicity *in vivo* is difficult, to say the least. Therefore it is also incumbent on the NTP to develop an *in vivo* model in an appropriate species to assure that the results of *in vitro* assays can be used to assess the relevance of photogenotoxicity assays.

Conclusions

The available toxicology and exposure information demonstrate that Red 27/28 do not meet the criteria for inclusion in the NTP testing program. We respectfully request that Red 27/28 be removed from consideration, and that the resources that would have been assigned to testing these color additives be re-assigned to substances that meet the NTP's criteria for inclusion in their testing program.

If NTP decides to proceed with testing Red 27/28, we request that NTP fully describe the protocols to be employed in the testing, and provide an opportunity for public review of the protocols.

Thank you for your consideration of our comments.

Sincerely,

Glenn Roberts
Executive Director